Case Report

PANCYTOPENIA SECONDARY TO AUTOIMMUNE VITAMIN B_{12} DEFICIENCY IN GRAVES DISEASE

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ABSTRACT

Objective: To describe a case of Graves disease (GD) and coexistent pancytopenia associated with autoimmune vitamin B_{12} deficiency. While thyrotoxicosis and antithyroid drugs can cause pancytopenia, other autoimmune conditions such as vitamin B_{12} deficiency can occur, leading to severe anemia and pancytopenia.

Methods: A 19-year-old female with GD treated with methimazole presented with thyrotoxicosis and evidence of pancytopenia. Diagnostic studies included a complete blood cell count, peripheral blood smears, thyroid function tests, and a bone marrow biopsy.

Results: White blood cells were 2.4×10^9 cells/L (reference range [RR] is 3.4 to 9.6×10^9 cells/L), hemoglobin was 7.9 g/dL (RR is 11.6 to 15.0 g/dL), neutrophil count was 1.2×10^9 cells/L, and platelets were 84×10^9 cells/L (RR is 157 to 371×10^9 cells/L). Thyroid-stimulating hormone was <0.01 mIU/L (RR is 0.50 to 4.30 mIU/L), free thyroxine was 3.7 ng/dL (RR is 1.0 to 1.6 ng/dL), and total triiodothyronine was 221 ng/dL (RR is 91 to 218 ng/dL). Due to suspicion for drug-induced pancytopenia, methimazole was discontinued. Three days later, she was hospitalized for a syncopal episode with a further decline in hemoglobin to 6.7 g/dL, neutrophils to 0.68×10^9 cells/L, and platelets to 69×10^9 cells/L. Bone marrow biopsy findings showing marrow hypercellularity and hypersegmented neutrophils suggested vitamin B_{12} deficiency. Vitamin B_{12} was <70 ng/L (RR is 180 to 914 ng/L). Intramuscular vitamin B_{12} injections were initiated, and pancytopenia resolved within 1 month.

Conclusion: Although rarely described in the literature, autoimmune vitamin B_{12} deficiency can be missed as an underlying etiology for pancytopenia in patients with GD. The clinical picture can be further confounded when these patients are treated with antithyroid drugs known to cause bone marrow suppression. **(AACE Clinical Case Rep. 2020;6:e282-e285)**

Abbreviations:
ATD = antithyroid drug; **GD** = Graves disease; **RR** = reference range; **WBC** = white blood cell

INTRODUCTION

Graves disease (GD) is an autoimmune process in which thyrotropin receptor antibodies stimulate thyrotropin receptors on the thyroid, leading to hyperthyroidism (1). Hyperthyroidism can affect all blood cell lineages through a variety of mechanisms leading to anemia, thrombocytopenia, leukopenia, and in rare instances pancytopenia(1-5). Likewise, use of antithyroid drugs (ATDs) for management of thyrotoxicosis is associated with a variety of hematopoietic abnormalities including agranulocytosis and pancytopenia (6,7). Achieving euthyroidism, or discontinuing the offending agent, often results in normalization of the hematologic disturbances. However, cytopenias in the presence of GD may in fact be attributable to co-occurring autoimmune processes such as celiac disease, pernicious anemia, or autoimmune hemolytic anemia (1,8,9).

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Acquired pernicious anemia is a rare autoimmune disease in which antibodies target and destroy parietal cells, leading to decreased production of intrinsic factor and subsequent vitamin B_{12} deficiency (10). Moderate to severe vitamin B_{12} deficiency can manifest with macrocytic anemia (pernicious anemia) or pancytopenia (11-14). It is estimated that pernicious anemia occurs in roughly 1 to 3% of patients with GD (8). Thus, maintaining a broad differential for the etiology of pancytopenia in GD is critical to successful management. Here, we present a rare case of pancytopenia associated with severe anemia secondary to autoimmune vitamin B_{12} deficiency in a young woman with GD treated with ATDs.

CASE REPORT

A 19-year-old, Caucasian female was evaluated in the clinic for a 1-year history of bilateral ankle swelling, pruritus, exophthalmos, unintentional weight loss of 9 kg, and intermittent nausea and vomiting. Laboratory tests demonstrated a thyrotropin level <0.01 mIU/L (reference range [RR] is 0.50 to 4.30 mIU/L), free thyroxine >7.77 ng/dL (RR is 1.00 to 1.60 ng/dL), free triiodothyronine >20.0 pg/mL (RR is 2.8 to 4.4 pg/mL), thyrotropin receptor antibodies of 4.17 IU/L (RR is ≤1.75 IU/L), and thyroid peroxidase antibody level of 65 IU/mL (RR is <9.0 IU/mL). White blood cell (WBC) count was 4.2×10^9 cells/L (RR is 3.4 to 9.6×10^9 cells/L), hemoglobin was 11.6 g/dL (RR was 11.6 to 15.0 g/dL), mean corpuscular volume was 79.8 fL (RR is 78.2 to 97.9 fL), red blood cell distribution width was 18.9% (RR is 12.2 to 16.1%), platelet count was 147×10^9 cells/L (RR is 157 to 371×10^9 cells/L), and neutrophils were 2.44×10^9 cells/L (RR is 1.56 to 6.45×10^9 cells/L). She was diagnosed with GD and started on methimazole at 10 mg twice daily, as well as propranolol at 20 mg twice daily.

Six months later, she presented with palpitations, tremors, heat intolerance, persistent nausea, vomiting, and occasional diarrhea. Although still prescribed methimazole, she had been taking it inconsistently. Physical examination revealed right eye lid retraction, a diffusely enlarged thyroid gland measuring approximately 45 g, and a normal cardiopulmonary examination. Her WBC count had declined to 2.4×10^9 cells/L, hemoglobin was 7.9 g/dL, mean corpuscular volume was 95.3 fL, neutrophil count was 1.2×10^9 cells/L, and platelet count was 84×10^9 cells/L. A peripheral blood smear showed no evidence of hemolysis or other abnormalities. Her thyrotropin was <0.01 mIU/L, free thyroxine was 3.7 ng/dL, total triiodothyronine was 221 ng/dL (RR is 91 to 218 ng/dL), and thyrotropin receptor antibodies were 4.17 IU/L. Due to suspicion for methimazole-induced agranulocytosis, methimazole was discontinued.

Three days later she was hospitalized for a syncopal episode and found to have a further decline in blood cell counts. There was no evidence of active bleeding or infection. Her WBC count had declined to 2.2×10^9 cells/L, hemoglobin to 6.7 g/dL, neutrophils to 0.68×10^9 cells/L, and platelets to 69×10^9 cells/L. Reticulocytes were 0.88% (RR is 0.60 to 2.71%) and absolute reticulocyte count was 17.6×10^9 cells/L (RR is 30.4 to 110.9×10^9 cells/L). A bone marrow aspiration and biopsy were subsequently performed revealing marked cellularity with erythroid predominance, slight left shift, occasional ringed sideroblasts, and decreased granulopoiesis with morphologically unremarkable megakaryocytes. These results were suggestive of vitamin B_{12} deficiency (Fig. 1).

The results of the bone marrow examination and a second peripheral blood smear were inconsistent with drug-induced pancytopenia (Fig. 2). Her vitamin B_{12} level was <70 ng/L (RR is 180 to 914 ng/L), serum folate was >20 μg/L (RR is ≥4 μg/L), and methylmalonic acid was 0.71 nmol/mL (RR is ≤0.40 nmol/mL). Subsequent serum testing confirmed the presence of anti-parietal cell antibodies, although intrinsic factor-blocking antibodies were negative. A diagnosis of vitamin B_{12} deficiency secondary to anti-parietal antibodies was made.

The patient received several units of packed red blood cells given the severity of her anemia, as well as 3 intramuscular doses of vitamin B_{12} (1,000 μg each). Her condition significantly improved, and she was discharged on a 1-month taper of glucocorticoids with weekly vitamin B_{12} injections for 2 months. After 1 month, all blood cell lines had normalized, with WBCs of 5.6×10^9 cells/L, hemoglobin of 12.4 g/dL, and platelets of 226×10^9 cells/L. She elected to undergo definitive therapy for GD with a total thyroidectomy. Two months after surgery, she was euthyroid on levothyroxine replacement therapy, and her blood cell counts remained normal on maintenance vitamin B_{12} injections monthly.

DISCUSSION

The coexistence of GD and pernicious anemia with associated pancytopenia has been infrequently reported, although epidemiological data suggest that the incidence of pernicious anemia is higher among patients with GD compared to the general population (8,9,15,16). In a cross-sectional study conducted in the United Kingdom, 1.4% of 2,791 patients with GD had coexisting pernicious anemia. In this study, females and males with GD were reported to have relative risks of pernicious anemia of 11.29 (95% confidence interval is 7.83 to 15.72) and 8.79 (95% confidence interval is 2.86 to 20.37), respectively (9).

In a community-based observational study, Furszyfer et al (16) reported that 7 out of 410 patients with GD were later diagnosed with pernicious anemia. All of the patients presented with thyrotoxicosis and hematologic abnormalities, although the earliest diagnosis of pernicious anemia was made 8 years after the GD diagnosis. This suggests the

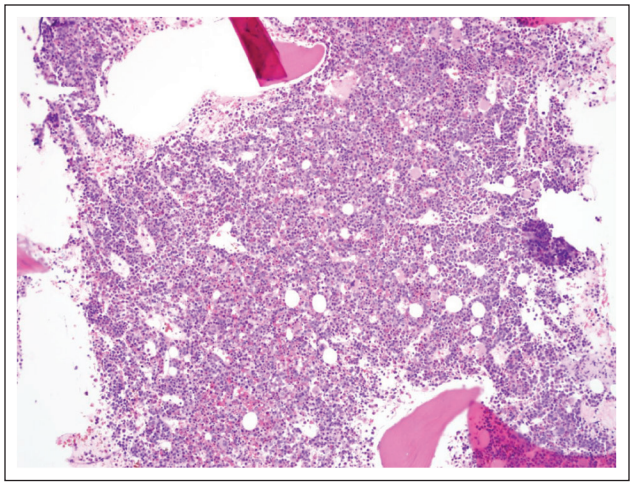

Fig. 1. Bone marrow biopsy.

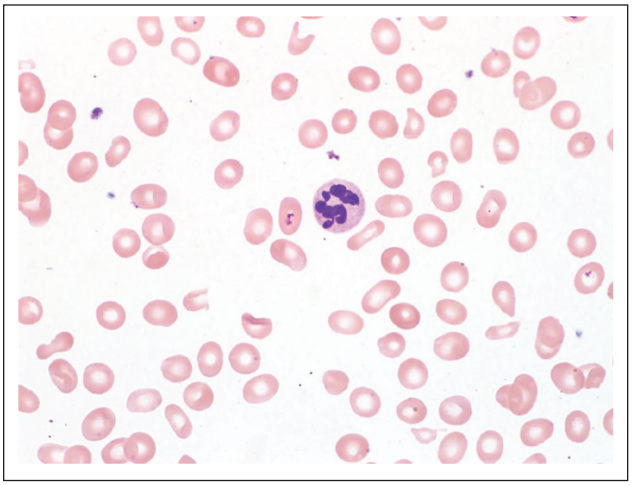

Fig. 2. Peripheral blood smear.

possibility of co-existent pernicious anemia at the time of GD diagnosis, which may have gone unrecognized, or may simply reflect the observed trends in age at time of diagnosis for each of these disorders.

Generally, the median age of pernicious anemia diagnosis is 60, while GD often presents earlier (17). Diagnosis of pernicious anemia prior to age 30 is rare and, indeed, only 1 patient in the above cohort was diagnosed with pernicious anemia prior to age 50 (16). Vitamin B_{12}, also known as cobalamin, is essential for blood cell division and maturation. In deficient states, macrocytic anemia is the first hematologic presentation. Progressive deficiency leads to bone marrow megaloblastic changes, hypercellularity, and dysplastic changes due to ineffective erythropoiesis leading to pernicious anemia. Pancytopenia has been described in the literature as part of cobalamin deficiency (11-14). Our patient represents the youngest patient described in the literature to be diagnosed with both pernicious anemia associated with neutropenia and thrombocytopenia or pancytopenia and GD concurrently.

Data are limited regarding the clinical and biochemical characteristics of patients who present with pancytopenia in the setting of coexistent GD and vitamin B_{12} deficiency. We identified 1 case report describing this scenario (18). The authors report on a 46-year-old male with GD being treated with propylthiouracil who developed pancytopenia while on ATD therapy. His WBCs were 3.7×10^9 cells/L, hemoglobin was 7.6 g/dL, and platelets were 80×10^9 cells/L. Due to concern for ATD-induced aplastic anemia, propylthiouracil was discontinued. However, the hematologic abnormalities persisted, thus prompting a bone marrow biopsy which revealed hypercellularity and megaloblastic changes, inconsistent with aplastic anemia. Further serologic evaluation confirmed vitamin B_{12} deficiency. Similar to our patient, all hematologic abnormalities resolved with administration of vitamin B_{12} (18).

In addition to underlying autoimmune disorders causing hematologic disturbances in the setting of GD, thyrotoxicosis itself can cause hematopoietic abnormalities, although pancytopenia is relatively rare. There have been 14 reported cases in the literature of pancytopenia associated with thyrotoxicosis in GD. Although the mechanisms remain to be fully delineated, it is hypothesized that pancytopenia results from either decreased production of hematopoietic cells or increased destruction (1). In our patient, pancytopenia nearly entirely resolved following treatment of the vitamin B_{12} deficiency, while thyrotoxicosis persisted. This suggested that the thyrotoxicosis itself was not the main contributor to the patient's unique presentation.

Confounding the clinical picture in our patient was the concurrent use of ATDs when pancytopenia was diagnosed. While agranulocytosis associated with ATD use occurs in approximately 0.1 to 0.5% of patients treated with these medications, the incidence of pancytopenia is reported to be even less (6,19). Agranulocytosis is thought to occur due to either direct toxic effects of ATDs on neutrophils or immune-mediated destruction, although the mechanisms pertaining to ATD-induced pancytopenia remain unclear (6,19). Use of methimazole in our patient, a drug known to cause myelosuppression, seemed to initially indicate a drug-induced pancytopenia. However, worsening pancytopenia despite discontinuation of methimazole, as well as the hematological findings of neutrophil hypersegmentation and bone marrow hypercellularity, were primary clues for the potential of a different etiology.

CONCLUSION

For patients with GD in whom pancytopenia fails to respond to traditional interventions such as discontinuation of ATDs, secondary causes for pancytopenia should be considered. Given the propensity for GD to coexist with other autoimmune conditions, vitamin B_{12} deficiency due to autoimmunity (anti-parietal cell antibodies) should remain on the differential diagnosis for these patients. Early testing and recognition of coexisting hematologic

disorders can expedite interventions and prevent adverse outcomes from delayed diagnosis.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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